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Mini-Reviews in Medicinal Chemistry, 2015, *15*, 000-000

Therapeutic Effects of Vitamin D in Asthma and Allergy

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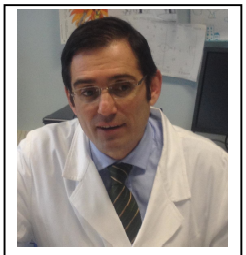

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Abstract: In recent years, low vitamin D status has been proposed as a putative risk factor for allergic diseases. A growing body of literature reports low vitamin D levels in atopic patients and supports an association between vitamin D deficiency and risk of adverse asthma and allergies outcomes. Therefore, it has been speculated that vitamin D supplementation may either prevent or reduce the risk of allergic diseases. Birth cohort studies addressing the role of vitamin D intake during pregnancy have shown conflicting results regarding allergy outcomes in offspring. Currently, only a few studies have tried to supplement vitamin D in asthmatic patients, often as an add-on therapy to standard asthma controller medications, and results are not all consistent. There is emerging data to show that vitamin D can enhance the anti-inflammatory effects of glucocorticoids and potentially be used as adjuvant therapy in steroid-resistant asthma. Recent *in vivo* data suggest that vitamin D supplementation may also reduce the severity of atopic dermatitis. This review examines the existing relevant literature focusing on vitamin D supplementation in the treatment of allergic diseases.

Keywords: Allergy, asthma, atopic dermatitis, food allergy, therapy, vitamin D.

1. INTRODUCTION

Over the past decade, a critical role for vitamin D (VD) in respiratory health and immune responses has been revealed [1]. Under these premises the supplementation of VD in the treatment of allergic diseases has emerged as a developing research field in recent years. Apart from the well-known role for VD in mineral and skeletal metabolism, there is evidence that this vitamin may be involved in the development of lungs and immune system during fetal and early post-natal life [2]. VD status seems to be closely related to immune responses against respiratory infections, which may exacerbate the frequency, severity and duration of asthmatic symptoms [3, 4]. Prospective studies have suggested that low maternal VD intake during pregnancy may increase the risk of childhood wheezing and asthma [5]. In children and adults with asthma, low VD status has been correlated with higher hospitalization rates along with increased corticosteroid use, airway hyper-responsiveness and impaired lung function [5, 6]. More recently, low VD status has also been proposed as a putative risk factor for atopic dermatitis (AD) and food allergy (FA) [7, 8].

The precise role of VD in the pathogenesis of asthma and allergic diseases is still debated and needs further assessment [3]. However, in light of emerging evidence of potential beneficial effects of VD, several trials have tested whether its supplementation could prevent or improve control of allergic diseases, particularly concerning asthma and AD.

Herein, we provide a review of the relevant literature addressing the role of VD supplementation in the prevention and treatment of allergic diseases.

2. VITAMIN D ACTIONS RELEVANT TO ASTHMA AND ALLERGIES

Despite the fact that different studies have reported an association between low VD status and allergic diseases, to date no study has completely described the mechanism of VD's actions in asthma and allergies [3].

VD has been observed to modulate immune responses and to have a role in the maturation of lungs, respiratory tract and skin [9-15]. Several cells intrinsic to innate and adaptive immunity, including B- and T-lymphocytes, macrophages and antigen-presenting cells, express the VD receptor which is the mediator of VD's effects [9, 16-19].

VD actions possibly relevant to asthma include up-regulation in lung tissues of antimicrobial peptides such as beta-defensins and cathelicidins, which have been shown to protect against respiratory tract infections that could trigger asthma [20-23].

The active form of VD, also referred to as 1,25-dihydroxyvitamin D (1,25(OH)2D), may decrease lung inflammation and airway hyper-responsiveness by promoting T-regulatory cell activity and down regulating synthesis of inflammatory cytokines in bronchial smooth muscle cells (such as matrix metalloproteinases and chemokine ligand 5,

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1389-5575/15 $58.00+.00

a chemo-attractant of mast cells, eosinophils, basophils and T-cells) [24-27]. There is evidence that 1,25(OH)2D can inhibit Th17 cytokines production, which is often increased in patients with severe asthma [28, 29]. There is also evidence that the active form of VD can affect the expression of genes involved in smooth muscle cell morphogenesis and growth, exerting anti-proliferative effects on the airway smooth muscle [30-33]. These findings suggest a possible involvement of VD in airway remodeling.

Recent experimental data suggest that VD can potentially increase response to glucocorticoids in steroid-resistant patients by up-regulating the IL-10 production from peripheral blood CD4+ T cells, which is commonly impaired in severe pediatric asthma [34, 35]. Indeed, peripheral CD4+ T-cells of steroid-resistant asthmatic patients have failed to synthesize the anti-inflammatory cytokine IL-10 in response to corticosteroids [36].

3. VITAMIN D IN THE TREATMENT OF ASTHMA

Epidemiologic studies have shown that VD deficiency and asthma are more prevalent in certain common conditions, such as darker skin pigmentation, inner-city residence and obesity, supporting the hypothesis of a causal association [2, 37, 38]. There is accumulating evidence to show that low VD status during pregnancy and early life is inversely correlated with the risk of developing upper and lower respiratory tract infections in childhood [5]. Respiratory viral infections (especially respiratory syncytial virus and rhinovirus infections) are considered as the main triggers of lower respiratory-tract wheezing illnesses (such as bronchiolitis) during infancy as well as asthma exacerbation through late childhood and have been strongly linked to the development of asthma [5]. Moreover, there is a growing body of evidence to show that serum VD levels below the proposed optimal range (defined as circulating levels of 25-hydroxyvitamin D, 25(OH)D, <30 ng/mL) in asthmatic children are associated with adverse asthma outcomes such as acute exacerbation, reduced lung function, increased corticosteroid use and poorer disease control [39-44]. In the light of these findings it has been speculated that VD supplementation may either prevent or reduce the risk of severe asthma and enhance response to glucocorticoids. Those hypotheses have led to a recent increase in the number of scientific publications concerning VD supplementation in allergic patients.

Birth cohort studies investigating the associations between VD intake during pregnancy and allergy outcomes in offspring have revealed conflicting results. Prospective studies have suggested that low maternal VD intake during pregnancy and low cord blood VD levels may increase the risk of childhood wheezing and respiratory infections in offspring [45-50]. On the other hand, conflicting results have been shown for asthma, with one study reporting an adverse effect on the risk of asthma development [50] and others showing no correlation [45, 51-53]. However, those studies are all limited either by having estimated maternal VD intake from food frequency questionnaires [46-50] or having only one measurement of 25(OH)D levels (in the pregnant mother or the cord blood) with a protracted interval to the considered outcomes [45, 51-53]. The Vitamin D Antenatal Asthma Reduction Trial is a randomized, double-blind, placebo-controlled (DBPC) trial of VD supplementation in pregnant women which is currently ongoing in the US to establish whether VD supplementation during pregnancy prevents the development of asthma and allergies in children [54].

Over the last decade several trials have assessed whether direct VD supplementation can be beneficial in the treatment of asthma (Table **1**).

In a double-blind parallel-arm trial conducted by Majack *et al.*, 48 children with newly diagnosed allergic asthma to house-dust mites were randomly assigned to either placebo or supplement of 500 IU/day of oral cholecalciferol (VD3) in addition to asthma controller medications (inhaled budesonide) for 6 months. At the end of the study period, children in the active group showed a reduced risk of asthma exacerbation triggered by acute respiratory viral infections [55].

In another randomized, DBPC study conducted on 82 Indian children with moderate to severe asthma, the monthly administration of 60.000 IU of oral VD3 in addition to standard steroid-based therapy for 6 months significantly reduced the number of acute exacerbation, emergency visits and the mean steroid dose to achieve asthma control [56].

In a very recent DBPC study conducted by Castro *et al.*, 408 adults with asthma and baseline serum 25OHD level <30 ng/ml were randomized to receive either placebo or high-dose oral VD3 (as 100.000 IU once followed by 4.000 IU/day) in addition to asthma controller medications (inhaled ciclesonide) for 28 weeks. In this study, VD supplementation significantly increased serum 25OHD levels and slightly reduced the dose of inhaled corticosteroid required to maintain asthma control, but it did not reduce either the rate of first treatment failure (defined as a combination of decline in lung function parameters and increase in use of β2-agonists, systemic corticosteroids and health care) or the number of acute exacerbation [57].

In another recent controlled trial by Arshi *et al.*, 130 children and adults with mild to moderate asthma were randomized in two groups. Both groups received asthma medications in a dry powder inhaler (budesonide, or budesonide plus formoterol) and one group was randomly chosen to further receive high-dose VD3 (100.000 IU intramuscularly as first dose, followed by 50.000 IU orally once a week) for 6 months. Serum VD levels and the spirometric parameter FEV1 were determined pre-trial and 8 and 24 weeks post intervention. At 8 weeks FEV1 improved in both groups with no significant difference. After 24 weeks, that FEV1 improved by about 20% in the VD group compared to about 7% among those who only used the inhaler. However, Arshi *et al.* did not consider whether the active group presented also an improvement in symptoms and whether this group was more adherent than controls to asthma medications [58].

Table 1. Summary of relevant trials on vitamin D supplementation in the treatment of asthma.

Author	Study type	Sample size	Intervention	Duration	Results
Majak *et al.*, 2011 [55]	Double-blind PC RCT	48 asthmatic children (5-18 years)	500 IU/day oral VD3 *vs* placebo, in addition to asthma control therapy (inhaled budesonide)	6 months	Reduced risk of asthma exacerbation triggered by acute respiratory tract infection in the VD group
Yadav *et al.*, 2014 [56]	Double-blind PC RCT	82 asthmatic children (5-11 years)	60.000 IU/month oral VD3 *vs* placebo, in addition to standard steroid-based therapy	6 months	Reduced number of asthma exacerbation ($P = 0.011$), emergency visits ($P = 0.015$) and decreased steroid dosage ($P = 0.013$) in the VD group
Castro *et al.*, 2014 [57]	Double-blind PC RCT	408 asthmatic adults (≥ 18 years)	100.000 IU bolus plus 4.000 IU/day oral VD3 *vs* placebo, in addition to asthma controllers (inhaled ciclesonide)	28 weeks	VD did not reduce the rate of first treatment failure (primary outcome, defined as combination of decline in lung function parameters and increase in use of β2-agonists, systemic corticosteroids and health care). VD slightly reduced the dose of inhaled corticosteroid required to maintain asthma control (difference of 14.9 μg/d).
Arshi *et al.*, 2014 [58]	PC RCT	130 asthmatic children and adults (10-50 years)	Asthma medications (budesonide or budesonide plus formoterol in a dry powder inhaler) with and without addition of 100.000 IU bolus (IM) plus 50.000 IU/week oral VD3	24 weeks	24 weeks after the intervention FEV1 improved by about 20% in the VD group compared to about 7% among those who only used the inhaler ($P < 0.001$).
Bar Yoseph *et al.*, 2014 [59]	Double-blind PC RCT	39 children (6-18 years) with mild non-treated asthma	14.000 IU/week oral VD *vs* placebo	6 weeks	No differences in relation to airway hyperreactivity parameters (i.e. FeNO and PC20-FEV1) and airways inflammation markers (i.e. exhaled breath condensate cytokines IL4, IL5, IL10, IL17, and γ-interferon) among the two groups.
Nanzer *et al.*, 2014 [64]	Double-blind PC RCT	24 adults (≥ 18 years) with steroid-resistant asthma	0.25μg calcitriol twice daily *vs* placebo, in addition to oral prednisolone (during the last 2 weeks)	4 weeks	Modest but significant improvement in absolute and predicted FEV1in the calcitriol group ($P = 0.03$).

Bar Yoseph *et al.* have recently conducted the first DBPC study to assess the potential role of VD as monotherapy in mild asthma. Over 6 weeks, a total of 39 children (age, 6-18 years) with mild non-treated asthma, positive methacholine test and serum 25OHD levels <30 ng/ml, were randomly assigned to either placebo or weekly supplements of 14.000 IU of oral VD (equivalent to 2.000 IU/day). At the end of the study period, despite a significant increase in serum 25OHD level in the active group, no differences were seen in relation to airway hyperreactivity parameters (i.e. fractional exhaled nitric oxide, FeNO and methacholine concentration causing a 20% reduction in FEV1, PC20-FEV1) and airways inflammation markers (i.e. exhaled breath condensate cytokines IL4, IL5, IL10, IL17, and γ-interferon) among the two groups [59].

Emerging experimental data provide evidence that VD can enhance the therapeutic response to glucocorticoids and potentially be used as an add-on treatment in steroid-resistant asthmatic patients [60]. Xystrakis *et al.* showed that the typical impaired production of IL-10 by CD4+ regulatory T cell observed in steroid-resistant asthmatic patients could be reversed by the addition of dexamethasone and VD [34]. In the same study the use of VD overcame the down-regulation of glucocorticoid receptor expression on CD4+ T cells induced by dexamethasone [34]. These findings are consistent with more recent *in vitro and in vivo* studies. In two cross-sectional studies conducted in children and adults with mild to moderate asthma, lower serum VD levels were associated with increased inhaled/oral corticosteroid use and impaired lung function [61, 62]. In a separate *in vitro* model of steroid-resistance, the same group of researchers showed that VD enhances glucocorticoids anti-inflammatory actions in peripheral blood mononuclear cells of patients with steroid-resistant and steroid-sensitive asthma [62, 63]. However, VD pretreatment did not overcome the reduced response to glucocorticoids in cells of patients with steroid-resistant asthma [63].

In a very recent *in vivo* DBPC pilot study, Nanzer *et al.* showed that the use of 1,25(OH)2D in adult patients with steroid-resistant asthma improved the clinical responsiveness to glucocorticoids. A total of 24 adults with steroid-resistant asthma (defined as less than 10% improvement in baseline FEV1 following a 2-week course of oral prednisolone) underwent a 4-week washout period and were subsequently randomized to either placebo or 0.25 μg of 1,25(OH)2D twice daily for 4 weeks. A repeat course of oral prednisolone

was given during the final 2 weeks of the study. At the end of the study period, the active group reported a modest but significant improvement in lung function (rated by absolute and predicted FEV1) compared to controls [64].

Three randomized controlled trials comparing lower (ranging from 200 to 400 IU/day) versus higher dose (ranging from 2000 to 4000 IU/day) of oral VD supplementation in VD-deficient asthmatic children are currently ongoing in Canada [65] and the US [clinicaltrials.gov, identifiers NCT02054975 and NCT01921894]. The aim of these studies is to assess the effects of high dose VD supplementation on serum VD levels, asthma severity and asthma exacerbation as well as to detect the most appropriate dose to be used in these patients.

4. VITAMIN D IN THE TREATMENT OF ATOPIC DERMATITIS

There is experimental evidence to show that the active form of VD can affect the growth and differentiation of keratinocytes as well as the production of antimicrobial peptides in the skin [11, 66-69]. The observation that keratinocytes express high levels of the enzyme 25OHD-1α hydroxylase, which is responsible for the activation of VD metabolites (as in the kidney), furthers supports these findings [69]. In addition, VD can stimulate the synthesis of different skin proteins (e.g. involucrine, transglutaminase, locricirin and filaggrin) enhancing the formation of the stratum corneum barrier [70]. Patients with AD often present a defect of the epidermal barrier and a relative defect in innate immunity, since they express lower levels of some antimicrobial peptides (such as cathelicidin) in areas of inflamed skin [71, 72]. Therefore low VD status might exacerbate AD by contributing to skin barrier function impairment and immunologic dysregulation.

Observational studies have documented that children and adults with AD often present significantly lower serum VD levels [73-75]. In a recent birth cohort study, low cord blood VD levels in 239 newborns were associated with higher risk of developing AD by the ages of 1, 2, 3, and 5 years [45]. Additionally, in children with AD a significant inverse relationship between the severity of the disease and serum VD levels has been shown [76].

Recent data have suggested a possible role for VD supplementation in the treatment of AD (Table **2**). In a small DBPC pilot study conducted by Sidbury *et al.*, 11 children (aged 2-13 years) with winter-related mild AD (according to the Eczema Area and Severity Index score, EASI) were randomized to receive either 1000 IU/day of oral ergocalciferol or placebo for 1 month, with the possibility to continue previous topical therapies but not to initiate new treatments. At the end of the study period, 4 of 5 children in the active group showed improvement according to the Investigator's Global Assessment Score, compared with 1 of 6 children taking placebo. A similar trend was also seen for the EASI score, but it failed to reach statistical significance [77].

The same group of researchers has recently conducted a similarly designed DBPC trial to evaluate the benefit of VD supplementation for winter-related AD in children living in Mongolia, a population known to have a high VD deficiency during winter season due to latitude. A total of 107 children, mostly with moderate AD according to the EASI score, were randomized to receive either 1000 IU/day of oral VD3 or placebo for 1 month. All participants were instructed to continue previous topical therapies as needed, but they were not allowed to begin any new treatment. At the end of the study period, the active group showed significant improvement in AD assessed with the EASI score (mean change -6.5 (SD 8.8) for VD group compared with -3.3 (SD 7.6) for placebo, $P = 0.04$) [78]. However, these two studies share some limitations, such as the inability to correlate clinical benefits with baseline VD levels (due to missing determinates of VD levels before and after supplementation), the short duration of the intervention and the very limited number of children with severe AD (only 6 participants in the second trial) [77-78].

In another DBPC study by Javanbakht *et al.*, 12 of 45 patients were randomized to receive 1.600 IU/day of oral VD3 for 2 months. At the end of the study period, the active group showed significant increase in serum VD levels and decrease in severity of the disease assessed with Scoring Atopic Dermatitis (SCORAD) index. The active group reported a higher improvement in SCORAD index than controls, but this difference was not statistical significant [79].

In a similarly designed trial, 60 patients with mild to severe AD (according to SCORAD index) were randomized to receive 1.600 IU/day of oral VD3 for 2 months. At the end of the study period, the active group showed a significant decrease in SCORAD index regardless of the initial severity of the disease [80].

Hata *et al.* recently conducted a randomized, DBPC study in adult patients with AD. A total of 76 subjects, 30 with moderate to severe AD (according to an average Rajka-Langeland score of 6), 30 non atopic controls and 16 subjects with psoriasis, were randomized to receive either 4000 IU/day of oral VD3 or placebo for 21 days. Serum 25OHD levels, skin cathelicidin levels and the EASI score were determined before and after the trial. At baseline more than 70% of AD patients had serum 25OHD levels below 30 ng/mL. After 21 days of oral VD supplementation, the active group showed an increase in mean serum 25OHD level, but no significant change in skin cathelicidin levels or EASI score [81].

A randomized DBPC trial in children (age, 2-17 years) with mild to severe AD (assessed with SCORAD index) is currently ongoing in Chile. Participants are randomized to receive either placebo or weekly oral VD3 supplementation with doses ranging from 8.000 IU to 16.000 IU according to their age (i.e. 8.000 IU/week between ages 2-5.9 years; 12.000 IU/week between ages 6-11.9 years; 16.000 IU/week between ages 12-17.9 years), for 6 weeks. The primary outcome is to verify whether this VD supplementation scheme can improve the clinical severity of AD rated by SCORAD index [clinicaltrials.gov, identifiers NCT01996423].

Table 2. Summary of relevant trials on vitamin D supplementation in the treatment of atopic dermatitis.

Author	Study type	Sample size	Intervention	Duration	Results
Sidbury *et al.*, 2008 [77]	Double-blind PC RCT	11 children (2-13 years) with mild AD (rated by EASI score)	1000 IU/day oral VD2 *vs* placebo Patients were allowed to continue previous topical therapies as needed, but not to begin new treatment.	1 month	Decreased severity of AD in the VD group rated by the IGA score ($P = 0.04$)
Javanbakht *et al.*, 2011 [79]	Double-blind PC RCT	45 patients with AD (rated by SCORAD index)	Group P (n = 11): oral VD and oral VE placebos; Group D (n = 12): 1600 IU/day oral VD plus VE placebo; Group E (n = 11): 600 IU/day oral VE plus VD placebo; Group DE (n = 11): 1600 IU/ day oral VD plus 600 IU/day oral VE	2 months	Group D showed significant increase in serum VD levels ($P < 0.001$) and decrease in severity of AD from baseline by 34.8% as rated by SCORAD ($P = 0.004$). This group showed a larger decrease in SCORAD index than the placebo group (28.9%), but this difference was not statistical significant.
Amestejani *et al.*, 2012 [80]	Double-blind PC RCT	60 patients with mild to severe AD (rated by SCORAD index)	1600 IU/day oral VD3 *vs* placebo	2 months	Decreased severity of AD in the VD group as rated by SCORAD index ($P < 0.05$)
Camargo *et al.*, 2014 [78]	Double-blind PC RCT	107 children (2 - 17 years) with mild to severe AD (rated by EASI score)	1000 IU/day oral VD3 *vs* placebo Patients were allowed to continue previous topical therapies as needed, but not to begin new treatment	1 month	Decreased severity of AD in the VD group rated by the EASI score (mean change - 6.5 (SD 8.8) for VD *vs* - 3.3 (SD 7.6) for placebo, $P = 0.04$)
Hata *et al.*, 2014 [81]	Double-blind PC RCT	76 adults: 30 with moderate to severe AD (rated by Rajka-Langeland score); 30 non-atopic controls; 16 with psoriasis	4000 IU/day oral VD3 *vs* placebo	21 days	Significant increase in mean serum 25OHD level in the VD group No significant change in skin cathelicidin, HBD-3, IL-13 and EASI score.

Several studies have recently assessed the effect of indirect VD replacement through heliotherapy or UV treatment for the management of AD, showing promising results [75]. Vähävihu *et al.* measured serum 25OHD levels and SCORAD Index in 23 Finnish adult patients with moderate AD before and after taking a 2-week course of heliotherapy. At the end of the study period, the authors reported a significant increase in serum 25OHD levels and decrease in SCORAD index in the majority of participants, with positive correlation between the two parameters [82].

5. VITAMIN D AND FOOD ALLERGY

Low VD status has recently been proposed as a putative risk factor for FA [83]. The VD hypothesis in FA comes from the observation of higher rates of FA or FA markers (such as cases of food-induced anaphylaxis and prescription rates of epinephrine auto-injector or hypoallergenic formulas) in geographic regions of Australia and the US with lower sunlight exposure as well as in children born during Autumn and Winter seasons [8]. Two recent large population-based studies have shown that low serum VD levels are associated with increased risk of peanut sensitization and challenge-proven peanut- or egg- allergy [84, 85]. In a very recent cross-sectional study conducted in 226 children (age, 3-24 months) with AD or suspected FA, Baek *et al.* confirmed that poly-sensitization to food allergens was correlated with lower serum 25(OH)D levels compared with mono-sensitization and non-sensitization [86].

However, not all studies support the VD hypothesis. Weisse *et al.* have recently described a positive association between maternal/cord blood VD levels and diagnosis of FA in the second year of life, even though it was a parent-reported doctor diagnosis of FA and not challenge-proven [87]. In addition, Norizoe *et al.* recently reported that maternal VD supplementation (800 IU/day of oral VD3 for 6 weeks) during the first months of lactation was correlated with higher rate of doctor diagnosed FA up to 2 years of age, although there was a significant loss of participants at the 2 year-old follow up [88].

To date, there is little evidence to support the association of low VD status and FA and well-designed trials on VD supplementation are needed to dissect its potential role in the prevention or treatment of FA. To this purpose, the VITALITY trial has been designed to assess whether VD supplementation during the first 10 months of life (as 400 IU/day of oral VD3) significantly decreases the risk of early onset FA. The study is not yet open for participants recruitment and it will be based in Australia [clinicaltrials.gov, identifiers NCT02112734].

6. CONCLUSION

There is evidence that serum VD level is often under the proposed optimal range in allergic children. In this population VD supplementation has proven to be effective in increasing serum 25(OH)D level. There is also accumulating evidence that low VD status may have a role in asthma and AD. It has been speculated that VD supplementation may prevent asthma or reduce the risk of a more severe disease and enhance response to corticosteroids as well as reduce the severity of AD. However, none of these hypotheses have been verified so far. Despite emerging *in vitro* and *in vivo* findings of the potential role of VD in the therapy of allergic diseases, only a few studies have actually tried to supplement VD as a treatment for asthma and AD, but results are not all consistent. This discrepancy can be at least in part attributed to the heterogeneity among different studies in terms of patients selection, inclusion criteria, VD dosing regimen, treatment dosage and duration, and outcomes considered. A different genetic predisposition among allergic patients might also affect the success of VD supplementation. Finally, a crucial issue for VD supplementation concerns its dosage. The currently recommended optimal levels of circulating serum 25(OH)D are referred to bone health, whereas the optimal levels for immune system function, defense against respiratory tract infections and treatment of allergic diseases are still unknown.

Further clinical trial results are needed to provide conclusive evidence and to identify the optimal dosage, length of treatment and target serum VD level for immune system functioning, allergic diseases prevention or treatment and for the use of VD in steroid resistant asthma.

LIST OF ABBREVIATIONS

AD	=	atopic dermatitis
DBPC	=	double-blind, placebo-controlled
EASI	=	eczema area and severity index
HBD-3	=	Human Beta Defensin 3
IGA	=	investigator's global assessment
IM	=	intramuscular
FA	=	food allergy
FeNO	=	Fractional exhaled nitric oxide
FEV1	=	forced expiratory volume in 1 second
PC RCT	=	placebo-controlled, randomized clinical trial
PC20-FEV1	=	methacholine concentration causing a 20% reduction in FEV1
SCORAD	=	SCORing Atopic Dermatitis
VD	=	vitamin D
VD2	=	ergocalciferol
VD3	=	cholecalciferol
VE	=	vitamin E (synthetic all-rac-α-tocopherol)
25(OH)D	=	25-hydroxyvitamin D
1,25(OH)2D	=	1,25-dihydroxyvitamin D

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

We are grateful to Maurice Fitzgerald for editing the English version of the manuscript.

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Received: March 20, 2014 Revised: April 16, 2014 Accepted: April 20, 2014